Enhanced trophic factor secretion by mesenchymal stem/stromal cells with Glycine-Histidine-Lysine (GHK)-modified alginate hydrogels.

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Public Summary:
Recombinant proteins and cytokines are under broad preclinical and clinical investigation to promote angiogenesis, but their success is limited by ineffective delivery, lack of long-term stability and excessive cost. Mesenchymal stem/stromal cells (MSC) secrete bioactive trophic factors, and thus, may provide an effective alternative to address these challenges. Glycine-Histidine-Lysine (GHK) is a peptide fragment of osteonectin, a matricellular protein with reported proangiogenic potential. We examined the capacity of GHK to up-regulate secretion of proangiogenic factors from human MSC in culture and when covalently coupled to alginate hydrogels. GHK had no apparent cytotoxic effects on MSC in culture over a wide range of concentrations. We detected a dose-dependent increase in vascular endothelial growth factor (VEGF) concentration in media conditioned by GHK-treated MSC, which increased endothelial cell proliferation, migration and tubule formation. We covalently coupled GHK to alginate using carbodiimide chemistry, and human MSC were entrapped in alginate hydrogels to assess VEGF secretion. Similar to monolayer culture, MSC responded to GHK-modified gels by secreting increased concentrations of VEGF and basic fibroblast growth factor compared to unmodified gels. The pre-treatment of MSC with antibodies to α6 and β1 integrins prior to entrapment in GHK-modified gels abrogated VEGF secretion, suggesting that the proangiogenic response of MSC was integrin-mediated. These data demonstrate that the proangiogenic potential of MSC can be significantly increased by the presentation of GHK with a biodegradable carrier, therefore increasing their clinical potential when used for tissue repair.

Scientific Abstract:
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